

Time to Deterioration in Quality of Life Score as a Modality of Longitudinal Analysis in Patients with Breast Cancer

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ABSTRACT

Purpose. This prospective multicenter study explored different definitions of time to deterioration (TTD) in quality of life (QoL) scores, according to different cut-offs of the minimal clinically important difference (MCID) as a modality for longitudinal QoL assessment in breast cancer patients.

Methods. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR-23 before surgery, after surgery, and 6 and 12 months later. The global health score, arm symptoms score (BRAS), and breast symptoms score were analyzed. For a given baseline score, QoL was considered to have deteriorated if this score decreased by ≥ 5 points at any time point after

baseline. Analyses were repeated using an MCID of 10 points and taking the score after surgery as the reference score (to explore the occurrence of response shift). TTD was calculated using the Kaplan–Meier method and Cox regression was used to identify independent factors associated with TTD.

Results. Two hundred thirty-five patients underwent axillary lymph node dissection (ALND), 222 underwent sentinel lymph node biopsy (SLNB), and 61 underwent SLNB plus ALND. Patients who underwent SLNB had a significantly longer TTD for the BRAS dimension than those who underwent ALND. Cox multivariate analyses showed that treatment using SLNB and age > 59 years were independently associated with longer TTD for the

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BRAS, whereas surgery elsewhere than at the Centre Georges François Leclerc was associated with a shorter TTD.

Conclusion. Exploration of different definitions of TTD in QoL provides meaningful longitudinal QoL results for clinicians. *The Oncologist* 2011;16:1458–1468

INTRODUCTION

In cancer research, the number of studies that incorporate quality of life (QoL) has been growing over the last decade [1]. Although the number of cancer clinical trials that include QoL assessment is increasing, there is also evidence that analysis of QoL presents methodological and statistical difficulties because of the type of data generated and the multidimensional nature of the instruments. One of the major concerns has been missing data [2]. Indeed, in longitudinal studies, observations of patients can be missed at certain time points because they miss visits or do not fill in certain questionnaires. In these cases, the interpretation of results for QoL can be seriously hampered by these missing data. Many publications have proposed methods for the collection, analysis, and interpretation of health-related quality of life (QoL) data [3–7]. Although these are useful to researchers and clinical trial investigators devoted to QoL research, some methods present statistical analyses and results that are difficult for physicians to use and interpret. Thus, there is a need to define a standard analysis of QoL data and presentation of results in ways that are clinically meaningful and deal with missing data. Indeed, QoL results must help clinicians in decision making while keeping the strength of the analyses [8].

The aim of this study was to explore definitions of time to deterioration (TTD) in QoL scores as a modality of longitudinal QoL assessment in breast cancer (BC) patients undergoing different surgical procedures, according to different cutoffs of the minimal clinically important difference (MCID).

PATIENTS AND METHODS

Patients

The design of this study has been described elsewhere [9]. Briefly, it was a multicenter prospective cohort study including all women operated on for BC as the primary treatment in five hospitals of the Côte d'Or and Saône-et-Loire. Patients underwent axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) according to the usual practice of the surgeon. A third group was defined for patients who underwent SLNB with additional lymphadenectomy. Cases were registered from January 2005 to January 2006.

All patients signed a written informed consent form and

the protocol of the study was approved by the regional ethics committee.

QoL

QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and the EORTC QLQ-BR23 [10] before surgery, just after surgery, and 6 and 12 months later. QoL was assessed at 12 months because the purpose of this study was to assess the early impact of surgical modality on QoL. We assessed QoL at these specific times based on clinical meaning in order to focus on the impact of surgery at 1 year with a feasible pragmatic collection of QoL data.

The global health score (GHS), arm symptoms score (BRAS), and breast symptoms score (BRBS) were targeted for analyses. The QLQ-C30 is a cancer-specific tool composed of 30 items that generate 15 scores: five scores of functional parameters, a financial difficulties scale, and eight scores for symptoms. The BC module is comprised of 23 questions assessing disease symptoms and side effects of treatment.

These scores vary from 0 (worst) to 100 (best) for the GHS and from 0 (best) to 100 (worst) for symptom parameters.

Statistical Methods

Continuous and qualitative variables are described using means, standard deviations, medians, and percentages. Patient characteristics are described according to the baseline completion of the questionnaire in order to determine non-random missing patient profiles. We also reported baseline QoL scores according to type of surgery. Then, analyses were done in patients with QoL completion at baseline.

TTD was defined as the time from inclusion in the study to deterioration in the following scores: GHS, BRAS, and BRBS. Patients were considered to have deteriorated for a given dimension if a decrease ≥ 5 points (5% of the theoretical score range) at any time point after baseline [5] was observed. Patients were censored at the time of the last QoL assessment completed if they had not deteriorated before that. All patients who had a baseline and at least one follow-up QoL assessment were included in the TTD analysis. Analyses were also performed for events defined as the first

5-point decrease in at least one of the following scores: GHS, BRAS, or BRBS.

Sensitivity analyses were performed to assess different definitions of TTD. Analyses were repeated for two other models: (a) considering patients to have deteriorated if the change in their score from baseline was ≥ 10 points [5] and (b) considering the score just after surgery as the reference score to integrate the occurrence of a response shift [11]. Analyses were also performed in which missing values were considered events.

TTD was calculated using the Kaplan–Meier method and compared using the log-rank test according to type of surgery. TTD is described using medians with 95% confidence intervals (CIs). The univariate Cox model was used to calculate the hazard ratio (HR) with 95% CI. Multivariate Cox regression, with type of surgery and other covariates, was applied to identify independent factors associated with TTD for each symptom. All variables with a univariate p -value $\leq .20$ from the Cox univariate analyses were eligible for multivariate analyses. Correlations were tested for eligible variables. To prevent collinearity, when two variables were significantly correlated, one variable was retained according to its clinical relevance or to the value of the likelihood ratio. The type of surgery and the hospital of treatment were forced into the multivariate analyses. All tests were two sided, and analyses were performed with Stata, version 11 software (StataCorp LP, College Station, TX).

RESULTS

Patients

Between January 1, 2005 and January 1, 2006, 518 BC patients were included. Two hundred thirty-five patients underwent ALND, 222 patients underwent SLNB, and 61 patients had SLNB with complementary ALND. Patient characteristics according to surgery group are detailed elsewhere [9].

QoL Scores at Baseline and Compliance

Three hundred eleven patients (60%) completed the QoL questionnaire at baseline, 354 (68%), 428 (83%), and 412 (80%) completed the QoL questionnaire after surgery, 6 months, and 12 months later, respectively. Patient clinical and pathologic characteristics, according to QoL completion at baseline, are presented in Table 1. At baseline, patients who completed the QoL questionnaires and those who did not were similar for most clinical characteristics except for hospital: hormonal status ($p = .44$), hormonal replacement therapy ($p = .14$), histoprognostic Scarff–Bloom–Richardson grade ($p = .31$), c-erb-2 status ($p =$

.89), hormone receptor status ($p = .1$), tumor histology ($p = .97$), hospital ($p < .0001$). In fact, the proportion of patients who did not complete a QoL questionnaire at baseline was higher in women treated in Châlon sur Saône Hospital and the Centre Georges François Leclerc (CGFL). Despite this unique difference, the mean QoL scores at baseline were similar in all domains (Table 2).

QoL TTD Analyses

The results in Table 3 show that a TTD ≥ 5 points in QoL score differed according to type of surgery only for the BRAS (Fig. 1). In fact, 92 patients in the ALND group, 86 patients in the SLNB group, and 21 patients in the SLNB plus ALND group experienced a TTD ≥ 5 points. The median TTD in the BRAS was 2.4 months (95% CI, 2.0–6.1 months) in the ALND group, 7.2 months (95% CI, 3.7–12.9 months) in the SLNB group, and 7.3 months (95% CI, 2.5–13.6 months) in the SLNB plus ALND group (log-rank $p = .011$). Compared with the ALND group, the univariate hazard ratios (HRs) were 0.64 (95% CI, 0.48–0.86) and 0.70 (95% CI, 0.44–1.13) for the SLNB and SLNB plus ALND groups, respectively.

For the GHS, 81 patients in the ALND group, 90 patients in the SLNB group, and 22 patients in the SLNB plus ALND group experienced a deterioration ≥ 5 points. The median TTD ≥ 5 points in the GHS was 6.6 months (95% CI, 2.4–7.7 months) for patients who underwent ALND, 6.7 months (95% CI, 3.26–11.9 months) for patients in the SLNB group, and 6.8 months (95% CI, 2.0–13.0 months) for patients in the SLNB plus ALND group (log-rank p -value = .66). Compared with the ALND group, the univariate HRs were 0.87 (95% CI, 0.64–1.18) and 0.98 (95% CI, 0.61–1.58) for the SLNB and SLNB plus ALND groups, respectively.

For the BRBS, 59 patients in the ALND group, 53 patients in the SLNB group, and 22 patients in the SLNB plus ALND group experienced a deterioration ≥ 5 points. The median TTD in the BRBS was 12.2 months (95% CI, 11.0 to not reached [NR]), 12.2 months (95% CI, 11.7 to NR), and 9.7 months (95% CI, 6.1–12.2 months) for the ALND, SLNB, and SLNB plus ALND groups, respectively (log-rank $p = .059$). Compared with the ALND group, the univariate HRs were 0.89 (95% CI, 0.61–1.29) and 1.57 (95% CI, 0.96–2.57) for the SLNB and SLNB plus ALND groups, respectively.

Cox multivariate analyses (Table 4) showed that treatment with SLNB (HR, 0.42; 95% CI, 0.19–0.95) and age > 59 years (HR, 0.63; 95% CI, 0.45–0.87) were independently associated with a longer TTD for the BRAS, whereas, surgery elsewhere than at the CGFL (HR, 1.48; 95% CI, 1.006–2.18) was associated with a shorter TTD.

Table 1. Characteristics of patients according to the completion of a quality of life questionnaire at baseline

	Patients who completed questionnaire at baseline (n = 311)		Patients who did not complete questionnaire at baseline (n = 207)		Fisher exact test p-value
	n	(%)	n	(%)	
Hormonal status					
Premenopausal	83	26.7	64	31	.44
Postmenopausal	277	73	143	69	
Unknown	1	0.4	0	0	
Hormone replacement therapy					
Yes	71	62	33	16	.14
No	193	23	137	66.1	
Unknown	47	15	37	17.9	
Histoprognostic Scarff–Bloom–Richardson grade					
1	90	28.9	49	23.7	.31
2	118	37.9	75	36.2	
3	67	21.6	50	24.2	
Unknown	36	11.6	33	15.9	
C-erb-2 status					
Yes	32	69.4	22	67.6	.89
No	216	10.3	140	10.6	
Unknown	63	20.3	45	21.7	
Hormone receptor status					
Yes	229	73.6	135	65.2	.1
No	44	14.2	36	17.4	
Unknown	38	12.2	36	17.4	
Tumor histology					
Invasive ductal	254	81.7	165	79.7	.97
Invasive lobular	22	7	15	7.3	
In situ	21	6.8	16	7.7	
Other	3	1	2	1	
Unknown	11	3.5	9	4.3	
Hospital					
Centre Georges François Leclerc	202	65	174	84.0	<.0001
Private hospital	46	14.8	16	7.8	
Le Creusot	29	9.3	0	0	
Macon	25	8.0	1	0.5	
Chalon sur Saône	9	2.9	16	7.7	
	Mean	SD	Mean	SD	Mann–Whitney p
Age	59.58	11.59	59.71	12.4	.84
Tumor size (mm)	16.5	12.99	17.41	13.72	.66
Duration of HRT (yrs)	1.83	4.28	1.52	3.77	.2

Abbreviations: HRT, hormone replacement therapy; SD, standard deviation.

Table 2. Quality of life at baseline according to type of node dissection

QLQ-C30 score	n	ALND group (235 patients)			n	SLNB group (222 patients)			n	SLNB + ALND group (61 patients)			Kruskal–Wallis p-value
		Mean (SD)	Median	Min–max		Mean (SD)	Median	Min–max		Mean (SD)	Median	Min–max	
Global health	119	74.5 (18.83)	83.34	16.67–100	156	76.60 (16.53)	83.34	33.33–100	34	76.71 (17.01)	83.34	33.33–100	.7734
Arm symptoms	117	6.08 (8.81)	0	0–33.33	157	7.50 (13.33)	0	0–66.67	34	8.82 (14.16)	0	0–55.56	.7035
Breast symptoms	133	18.86 (15.92)	16.67	0–66.67	150	20.94 (17.64)	16.67	0–83.34	37	18.02 (19.89)	16.67	0–91.67	.2882

Abbreviations: ALND, axillary lymph node dissection; QLQ, quality of life questionnaire; SD, standard deviation; SLNB, sentinel lymph node biopsy.

Table 3. Time to deterioration ≥ 5 points in quality of life score according to type of node dissection

	n	Deterioration (events)	Median	95% CI	Log-rank p-value	Cox univariate HR	95% CI	p-value
Global health score								
ALND group	117	81	6.63	2.4–7.7	.659	1		
SLNB group	149	90	6.73	3.26–11.9		0.87	0.64–1.18	.383
SLNB + ALND group	31	22	6.86	2.06–13.03		0.98	0.61–1.58	.96
Arm symptoms score								
ALND group	115	92	2.4	2–6.1	.011	1		
SLNB group	148	86	7.2	3.76–12.96		0.64	0.48–0.86	.004
SLNB + ALND group	32	21	7.3	2.5–13.66		0.7	0.44–1.13	.155
Breast symptoms score								
ALND group	127	59	12.2	11.06–	.0594	1		
SLNB group	120	53	12.2	11.7–		0.89	0.61–1.29	0.546
SLNB + ALND group	33	22	9.77	6.1–12.2		1.57	0.96–2.57	0.068

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

When considering a deterioration (5 or 10 points as the MCID) of at least one score as an event, the TTD did not differ significantly according to type of treatment (supplemental online Fig. 1). The number of patients who experienced a deterioration ≥ 5 points in one of the three scores was 125 in the ALND group, 125 in the SLNB group, and 36 in the SLNB plus ALND group, with median TTD of 2.86 months (2.26–5.06 months), 3.56 months (2.03–6.1 months), and 5 months (2.0–6.0 months) for the ALND, SLNB, and ALND plus SLNB groups, respectively (log-rank $p = .45$). Multivariate Cox analysis showed that only treatment elsewhere than at the CGFL (HR, 1.47; 95% CI, 1.11–1.94) was independently associated with a shorter TTD for a 5-point decrease. For a 10-point decrease, treatment elsewhere than at the CGFL (HR, 1.44; 95% CI, 1.08–1.92) was independently associated with a shorter TTD, whereas age > 59 years (HR, 0.76; 95% CI, 0.60–0.98) was independently associated with a longer TTD.

The Kaplan–Meier probability curves for TTD ≥ 10 points in QoL scores are shown in Figure 2. For the GHS,

the TTD was not significantly different according to the type of surgery—HRs of 0.98 (95% CI, 0.70–1.37) and 1.09 (95% CI, 0.60–1.87) for the SLNB and SLNB plus ALND groups, respectively, compared with the ALND group. For the BRBS, the TTD was not significantly different according to type of surgery either—HRs of 0.69 (95% CI, 0.43–1.11) and 1.62 (95% CI, 0.91–2.89) for the SLNB and SLNB plus ALND groups, respectively, compared with the ALND group. However, the TTD was significantly shorter in the SLNB plus ALND group (log-rank $p = .017$) than in the SLNB group. The results were the same as those for a 5-point deterioration in the BRAS.

When the score after surgery was used as the reference, the TTD did not differ significantly according to type of surgery (log-rank $p = .751$ and 0.128 for the GHS and BRAS, respectively) (supplemental online Fig. 2).

When missing values were considered events for censored patients, the overall results did not differ significantly. Cox univariate analysis (supplemental online Fig. 3b) shows that SLNB was associated with a longer TTD than with ALND

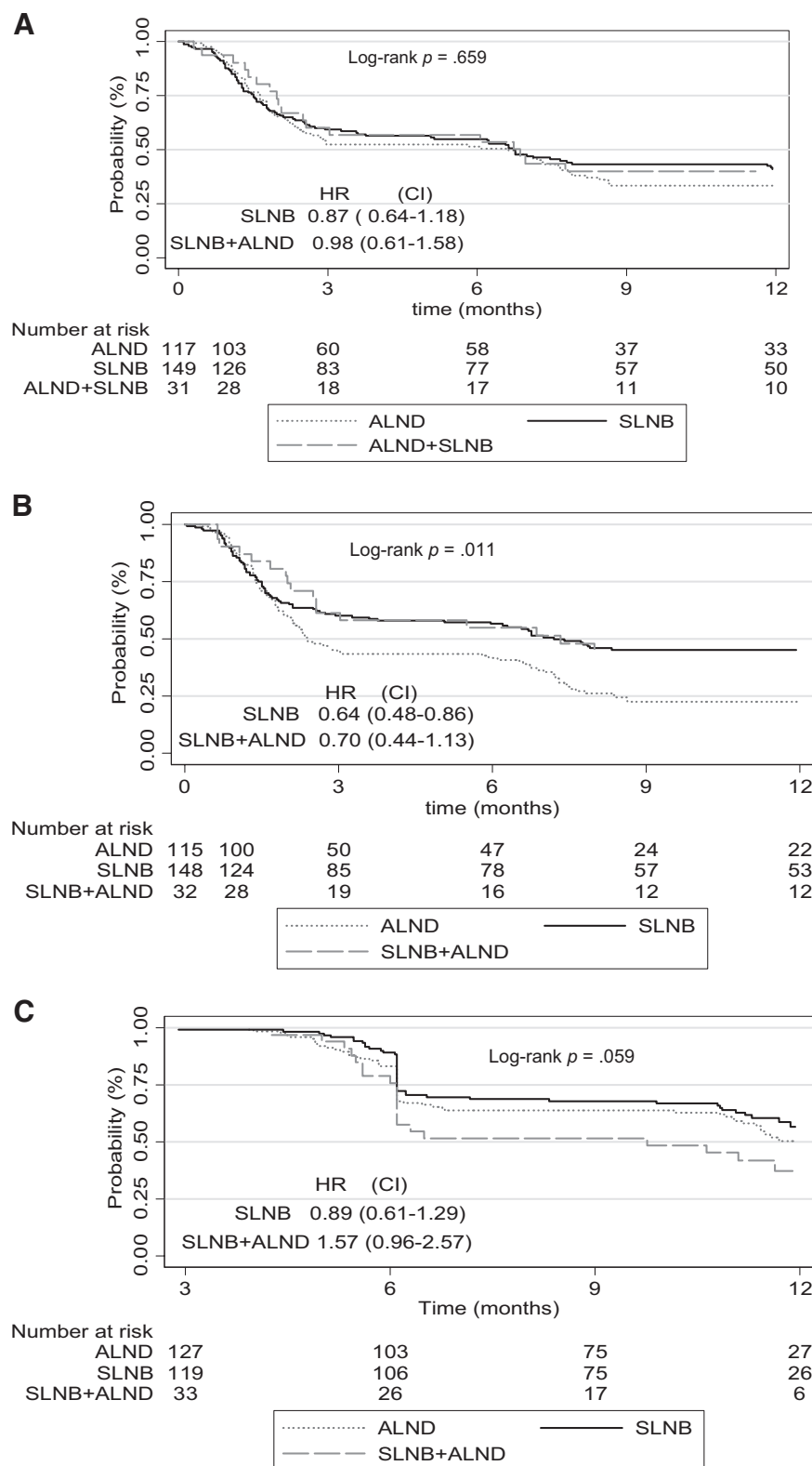


Figure 1. Time to a five-point deterioration in quality of life score. **(A):** Global health. **(B):** Arm symptoms. **(C):** Breast symptoms. Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

(HR, 0.72; 95% CI, 0.55–0.95) for arm symptoms. For the GHS ($p = .859$, supplemental online Fig. 3a) and BRBS ($p = .081$, supplemental online Fig. 3c), the TTD did not differ significantly according to treatment protocol.

Table 4. Multivariate Cox analysis for a 5- and 10-point deterioration

	5-point deterioration				10-point deterioration			
	<i>n</i> (events)	HR	95% CI	<i>p</i> -value	<i>n</i> (events)	HR	(95% CI)	<i>p</i> -value
Global health score								
Axillary dissection type	251 (163)				287 (150)			
ALND		1				1		
SLNB		0.92	0.63–1.35	.688		1.14	0.79–1.64	.467
ALND + SLNB		1.02	0.62–1.69	.909		1.14	0.67–1.96	.614
Hormone replacement therapy								
No		1						
Yes		1.24	0.88–1.74	.2		–	–	–
Tumor histology								
Invasive ductal		–	–	–		1		
Invasive lobular		–	–	–		0.87	0.48–1.59	.665
In situ		–	–	–		0.4	0.17–0.92	.032
Hospital								
CGFL		1				1		
Others		1.06	0.73–1.55	.737		1.01	0.69–1.47	.94
Positive nodes								
No		1				–	–	–
Yes		1.26	0.87–1.83	.208		–	–	
Age, yrs								
<59		1				1		
≥59		1.2	0.87–1.64	.249		1.24	0.89–1.72	.189
Arm symptoms score								
Axillary dissection type	245 (167)				245 (167)			
ALND		1				1		
SLNB		0.42	0.19–0.95	.039		0.42	0.19–0.95	.039
ALND + SLNB		0.73	0.43–1.24	.249		0.73	0.43–1.24	.249
Histoprognostic Scarff–Bloom–Richardson grade								
1		1				1		
2		1.12	0.74–1.68	.573		1.12	0.74–1.68	.573
3		1.05	0.66–1.67	.809		1.05	0.66–1.67	.809
Hospital								
CGFL		1				1		
Other		1.48	1.006–2.18	.046		1.48	1.006–2.18	.046
Mastectomy								
No		1				1		
Yes		1.02	0.65–1.59	.913		1.02	0.65–1.59	.913
<i>n</i> of nodes removed								
<5		1				1		
≥5		0.53	0.26–1.06	.07		0.53	0.26–1.06	.07
Positive nodes								
No		1				1		
Yes		1.04	0.77–1.50	.803		1.04	0.77–1.50	.803
Duration of hospitalization, days								
≤6		1				1		
>6		1.14	0.75–1.72	.537		1.14	0.75–1.72	.537

(continued)

Table 4. (continued)

	5-point deterioration				10-point deterioration			
	<i>n</i> (events)	HR	95% CI	<i>p</i> -value	<i>n</i> (events)	HR	(95% CI)	<i>p</i> -value
Tumor size, mm								
<15		1				1		
≥15		1.2	0.80–1.81	0.36		1.2	0.80–1.81	0.36
Age, yrs								
<59		1				1		
≥59		0.63	0.45–0.87	0.005		0.63	0.45–0.87	0.005
Breast symptoms score								
Axillary dissection type	235 (113)				279 (89)			
ALND		1				1		
SLNB		0.96	0.62–1.50	.885		0.63	0.35–1.12	.122
ALND + SLNB		1.55	0.89–2.70	.117		0.45	0.18–1.12	.089
Hormonal status								
Premenopausal		1						
Postmenopausal		0.74	0.49–1.13	.172		–	–	–
Hormone receptor status								
No		1						
Yes		0.69	0.43–1.12	.137		–	–	–
Hospital								
CGFL		1				1		
Other		1.09	0.68–1.74	.719		0.99	0.57–1.73	.994
Neoadjuvant chemotherapy								
No		1						
Yes		1.27	0.65–2.48	.481		–	–	–
<i>n</i> of nodes removed								
<5		–				1		
≥5		–	–	–		1.05	0.46–2.38	.905
Age, yrs								
<59		–				1		
≥59		–	–	–		0.74	0.48–1.13	.166
First decrease in one of the three scores								
Axillary dissection type	358 (286)				359 (263)			
ALND		1				1		
SLNB		0.77	0.59–1.01	.062		0.79	0.60–1.04	.09
ALND + SLNB		1.05	0.72–1.52	.791		0.97	0.65–1.45	.904
Hospital								
CGFL		1				1		
Other		1.47	1.11–1.94	.006		1.44	1.08–1.92	.012
Age, yrs								
<59		1				1		
≥59		0.82	0.65–1.04	.11		0.76	0.60–0.98	.034

Abbreviations: ALND, axillary lymph node dissection; CGFL, Centre Georges François Leclerc; CI, confidence interval; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

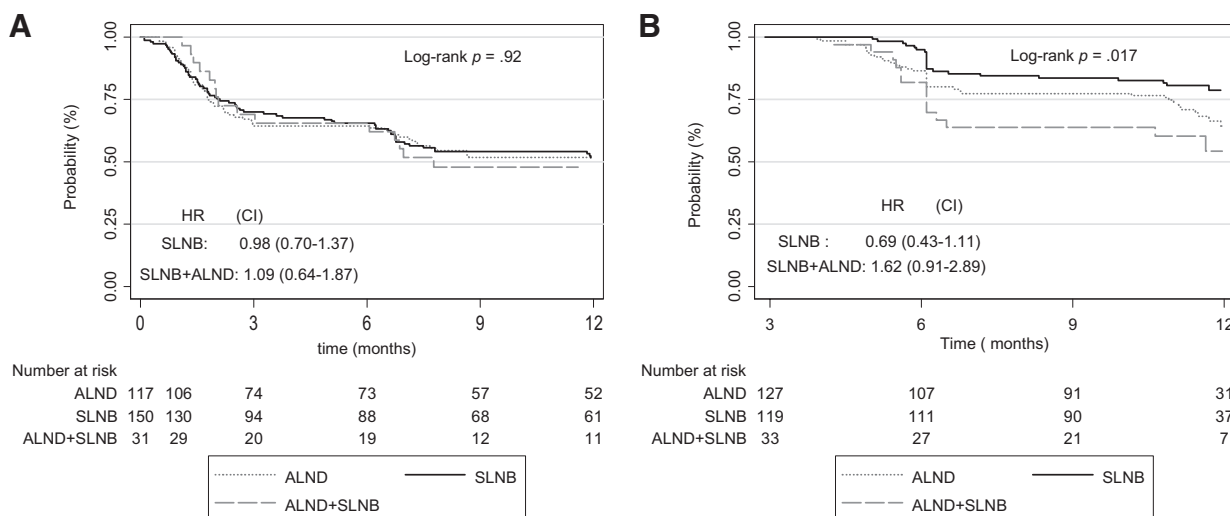


Figure 2. Time to 10-point deterioration in quality of life score. **(A):** Global health. **(B):** Breast symptoms.

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

DISCUSSION

In this study, we examined TTD as a method for longitudinal analysis of QoL in BC studies. We evaluated this method on data from a prospective multicenter study comparing the impact of three different surgical procedures on health-related QoL in patients with BC: SLNB, ALND, and SLNB plus ALND. QoL was assessed just after surgery and 6 and 12 months later, based on clinical meaning and on a pragmatic approach for this study. In fact, we believe that, at 6 or 12 months after surgery, patients could have recovered their baseline QoL level or shown a trend for QoL deterioration. Our study shows that, for the BRAS, women who underwent SLNB experienced a longer TTD than women who underwent ALND. Cox regression analyses showed that SLNB and age >59 years were independently associated with a longer TTD for the BRAS, whereas surgery elsewhere than at the CGFL was associated with a shorter TTD. This difference in the TTD for patients treated at CGFL compared with those treated at the other participating centers was probably a result of the fact that the CGFL is a comprehensive cancer care center with a high quality of care and because of the greater number of patients treated at this institution. In addition, when the study was performed, the learning curve for the SLNB surgical technique was complete at CGFL but it was ongoing at the other participating centers.

Our results are in agreement with those obtained with a mixed model analysis of variance for repeated measures. In every instance, the beneficial effect of SLNB on BC patient QoL, compared with ALND, was observed [9].

Previous nonrandomized and randomized [12–14] studies have already reported that SLNB is associated with less

arm and shoulder morbidity than with ALND. Moreover, our results show that, when considering the first five-point decrease in one of the three scores as an event, the TTD did not differ significantly according to type of treatment. This is explained by the difficulty in creating a single measure that aggregates the multiple dimensions of QoL and that is valid in all contexts. There is also potential for a particular intervention to produce benefits in one dimension and deficits in another that cancel each other out [10].

To assess how missing data could affect QoL results, in sensitivity analyses, patients were considered to have deteriorated when they did not have an assessment at a time point. This assumed that the reason for the missing data was the worsening of the patient's QoL. The results were only slightly different. In particular, for the BRAS, the TTD was still significantly shorter in patients who underwent ALND than in those who underwent SLNB.

In this study, the results for TTD were similar for a deterioration of five points and for a deterioration of 10 points. The small differences in the numbers of patients who deteriorated with a threshold MCID of five points compared with those experiencing deterioration with a threshold of 10 points indicate that, even with a five-point difference in QoL score, we could capture the information related to QoL deterioration. Based on our results, we suggest that a threshold MCID of five points is a clinically meaningful cutoff for event definition. Nonetheless, it is also important to underline that major differences in QoL deterioration could not be captured using a five-point difference in the QoL score. For example, our results showed a significant difference between the SLNB plus ALND group (log-rank $p = .017$) and the SLNB group for the BRBS QoL only when the deteri-

oration threshold was 10 points, suggesting differences for major QoL deterioration only.

One of the limits of our study is that a response-shift assessment had not been integrated in the design of the study. In fact, as reported by Bernard et al. [15], a response shift may attenuate estimates of treatment effects because of adaptation of the patient to the treatment or the disease. In this study, therefore, the occurrence of a response shift was assessed by changing the QoL reference score. The score just after surgery was used as the reference score rather than the inclusion QoL. The results showed no effect of treatment on TTD in all three QoL dimensions. As mentioned in the literature, changes in patients' internal standards, values, and the disease trajectory may distort the comparability of longitudinal assessments [15]. Although using the score just after surgery as the reference score could only be considered a surrogate method to assess response shift, we expected to have an overview of how QoL scores could vary over time when the reference is modified. The same issue exists with the Response Evaluation Criteria in Solid Tumors regarding the choice of reference for tumor measurement to capture progression or response (i.e., tumor measurement before treatment or nadir as the reference) [16]. However, another study to assess the impact of response shift on longitudinal QoL in patients with primary BC using the dedicated then-test method as the reference [17] is in progress.

Here, we used TTD in QoL as a conservative approach that took into account nonignorable missing data in cancer clinical trials [18]. Indeed, as can be expected in cancer clinical trials, a substantial proportion of patients often progress or deteriorate and withdraw from the study. The usual high attrition rate can be related to the treatment received and is a complicating factor in repeated-measures analysis of variance and interpretation of QoL data. The TTD approach is similar to other time-to-event analyses, such as time to progression, and has already been used in the analysis of QoL in other cancer locations [19–22]. TTD is less affected by missing data than is a classical analysis of variance. Patients can be kept in the analysis even if some of their questionnaires are missing as long as they have assessable questionnaires afterward. Moreover, because this is not an absorbing state, that is, it is not a time to definitive QoL deterioration, these results could help clinicians to de-

termine time frames for QoL deterioration and then to adapt the therapeutic strategy to improve QoL. One of the benefits of the TTD approach is that it provides results that are readily meaningful to clinicians and are more likely to influence clinical decision making. Other definitions are to be studied, including those that take into account the phenomenon of response shift or use appropriate methods to take account of intermittent missing data.

In conclusion, our study showed that, for the BRAS, women who underwent SLNB experienced a longer TTD than did women who underwent ALND. Furthermore, our results showed that for the GHS and BRAS QoL, there was no significant longitudinal difference between BC patients who underwent SLNB followed by a complementary ALND and those who underwent ALND alone. However, the TTD was significantly shorter in the SLNB plus ALND group than in the SLNB group for the BRBS dimension. One explanation could be that these patients underwent two operations and therefore had more postoperative side effects. In clinical practice, therefore, clinicians should be aware that the selection of patients for SLNB is critical for patient QoL. Although SLNB could improve QoL, complementary ALND could have a deleterious effect. Patients should thus be clearly identified to maintain the potential beneficial effect of this strategy.

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